REVIEW ARTICLE

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Liver Transplantation

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Liver transplantation, first performed in humans 60 years ago, has become the standard of care for patients with life-threatening liver disease (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). However, it remains a demanding therapy for patients, providers, and society. This article focuses on current developments in liver transplantation, particularly in adults, and briefly discusses issues that affect transplantation in children.

Challenges in Access to Liver Transplantation

Although in more than 100 countries at least one liver transplantation occurred in 2020–2021, worldwide, most patients with life-threatening liver disease do not have access to liver transplantation (Fig. S1).[1] In the United States, limited access to liver transplantation has been linked to Black race, poverty, rural residence, poor health literacy, or lack of medical insurance.[2-4] In 2022, there were 9528 liver transplantations in the United States, of which 526 were performed in patients under the age of 18 years.[5] Only 54.4% of transplant recipients received their graft within 1 year after placement on the transplant waiting list, and the rate of death among patients awaiting transplantation was 12.2 deaths per 100 waiting-list years.[3] Unfortunately, 5% of children placed on the waiting list die or are considered to be too ill to undergo transplantation; indeed, the highest pretransplantation mortality is among children under 1 year of age.[3]

Patient Referral, Assessment, and Selection for Liver Transplantation

Patients at risk for death from liver disease should be referred to a liver transplantation center. As shown in Figure 1, one presentation leading to a referral for transplantation is the onset of liver failure in a previously healthy person, manifested by a marked elevation in serum aminotransferase levels, altered mental status, and coagulopathy. The causes of acute liver failure are shown in Table S1. Acute liver failure accounts for less than 5% of liver transplantations performed annually in the United States.[3] The remaining transplantations are undertaken to treat patients with chronic fibrotic liver disease, portal hypertension, liver cancer, or a combination of these conditions (Table S1). The transition from clandestine cirrhosis with portal hypertension to clinically apparent liver disease with a reduced life expectancy is often heralded by the onset of a decompensating event such as new-onset ascites, altered mental status (hepatic encephalopathy), or gastrointestinal bleeding related to portal hypertension (Fig. 1).

In the United States, the Model for End-Stage Liver Disease (MELD) score, or the complementary Pediatric End-Stage Liver Disease (PELD) score for children under the age of 12 years, has been used since 2002 to assess the need for a liver transplant. Patients who have had a decompensating event or who have objective evidence of advanced chronic liver disease with a MELD score of 15 or higher (on a scale from 6 to 40, with higher scores indicating more severe liver failure) or a PELD score of 12 or higher should be referred for consideration for liver transplantation. The MELD and PELD scores, both of which are derived from objective clinical measures, are described in Table S2. Patients with cirrhosis should receive surveillance for hepatocellular carcinoma (HCC) with the use of abdominal imaging every 6 months. Suspicious liver masses discovered during surveillance are best managed by a multidisciplinary team that includes a liver transplantation team (Table 1, and Table S1).

The evaluation for liver transplantation comprises an assessment of urgency (on the basis of the prognosis without transplantation) and the impediments to a successful long-term outcome after transplantation (Fig. 2 and Table 1). The pretransplantation assessment includes a panel of tests that are individualized for each patient according to the diagnosis, degree of liver impairment, and risks associated with coexisting conditions.[6] During the evaluation, plans are made to mitigate coexisting conditions, assess infectious disease risks, and administer vaccinations that have not yet been received (Table S1).[7] The coronavirus disease 2019 (Covid-19) pandemic highlighted the importance of ensuring that vaccinations have been completed while a transplantation candidate is immunocompetent (i.e., before the administration of immunosuppressive therapy, which depresses responsiveness to vaccines).[8] In addition, all patients undergo a psychosocial assessment to determine whether they have the social support network and psychological health to sustain a transplant.[9] If patients have dual organ failure, a combined transplantation of liver with kidney, heart, or lung may need to be considered.

Since 2010, patients placed on liver transplant waiting lists in Western countries have tended to be older and more ill than patients in earlier eras.[3] In addition, since the introduction of direct-acting antiviral therapies in high-income countries, there has been a precipitous decline in the number of patients placed on the waiting list because of hepatitis C virus (HCV) infection, and alcohol-associated liver disease (ALD) and metabolic dysfunction–associated steatotic liver disease (MASLD), formerly called non–alcohol-related fatty liver disease, have become the predominant indications for liver transplantation.[3,10,11] In Asia, chronic viral hepatitis and virus-associated hepatocellular carcinoma continue to predominate among the diagnoses for patients on waiting lists.[12]

LIVING-DONOR LIVER TRANSPLANTATION

Living-donor liver transplantation offers a lifeline to patients with serious liver disease who are at high risk for death while waiting for a suitable liver transplant from a deceased donor (Table 2). Liver transplants from living donors account for 6% of all liver transplantations performed in the United States, whereas 90% of liver transplants in Asian countries other than China are from living donors (Fig. S1).[12] Outcomes after living-donor liver transplantation have been shown to be as good as or better than outcomes after deceased-donor liver transplantation, with a survival benefit accruing in patients with MELD scores as low as 11.[13,14] Unfortunately, in some countries in Asia, financial incentives appear to have spurred donation of solid organs by living persons.[15,16] Although donation of liver tissue is considered to be safe when undertaken at an experienced center, serious injuries to the physical or mental health of the donor, including death, have occurred on rare occasions.[17,18] Key aspects of living-donor liver transplantation are listed in Table 2 and described in the Supplementary Appendix.

RISK SCORES AND LIVER TRANSPLANTATION

In the United States, prioritization of patients awaiting transplants from deceased donors is guided by the federal final rule for transplanta-

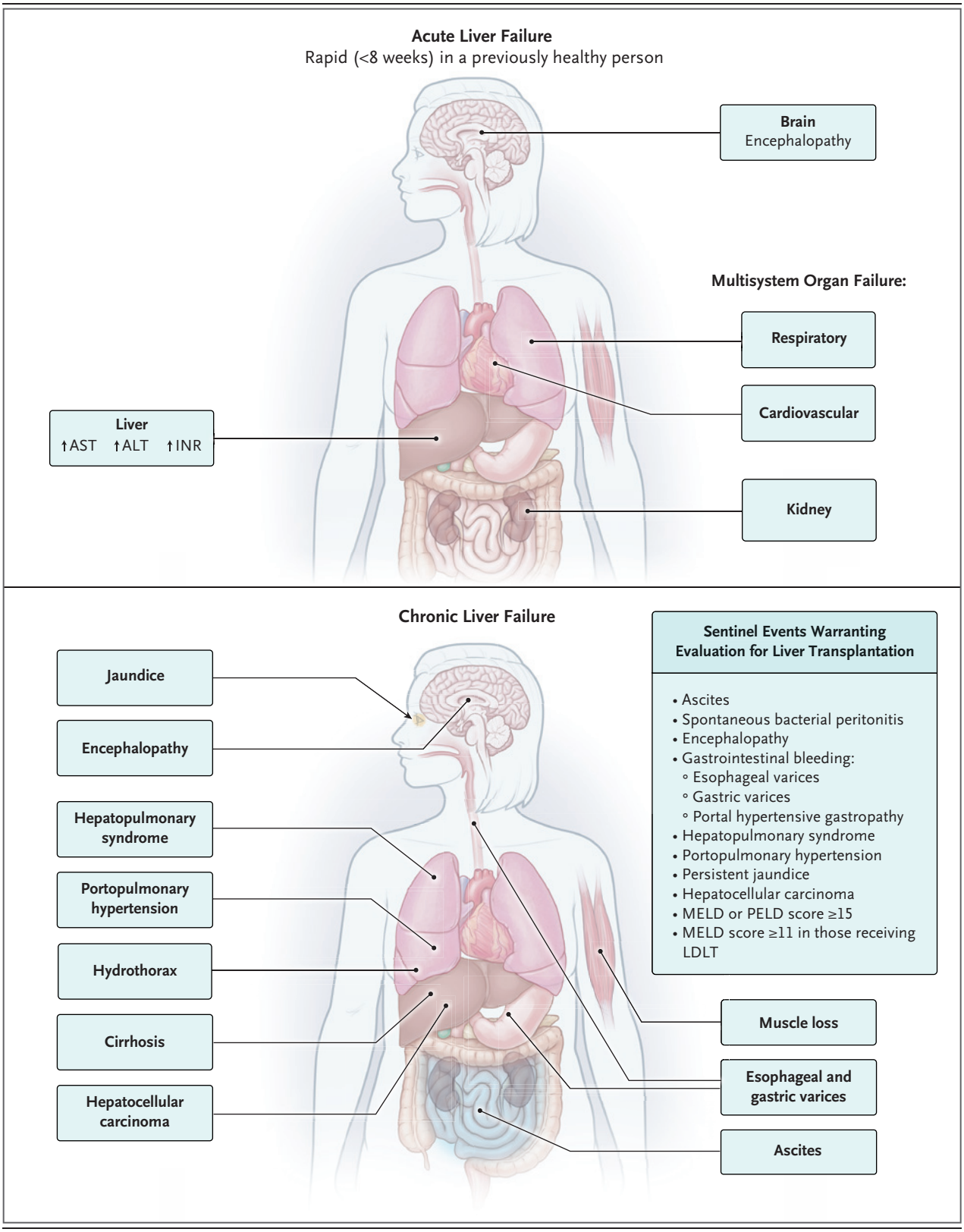

Figure 1 (facing page). Clinical States That Warrant Evaluation for Liver Transplantation.

Panel A shows a patient with acute liver failure; multiorgan failure occurs, with elevations in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and the international normalized ratio (INR). Panel B shows a patient with chronic liver failure. GI denotes gastrointestinal, LDLT living-donor liver transplant, MELD Model for End-Stage Liver Disease, and PELD Pediatric End-Stage Liver Disease.

tion, which dictates that transplantation centers must allocate donor livers on the basis of the greatest urgency, while negating inequities based on waiting time or geography and avoiding futile transplantation. The MELD and PELD scores have been the main tools for prioritizing patients on the waiting list (Table S2).[19,20] In contrast, in the United Kingdom, deceased-donor livers have been allocated since 2018 according to the anticipated benefit for the patient rather than urgency.[21]

The MELD score has undergone several modifications to improve accuracy and reduce bias (Table S2).[22,23] To increase the chance for transplantation, additional points may be added to the calculated MELD and PELD scores of waitlisted patients with specific conditions, such as HCC, portopulmonary hypertension, and the hepatopulmonary syndrome, disorders for which MELD and PELD fail to capture an accurate prognosis. There is a national review process for patients whose calculated MELD or PELD scores appear to underestimate how urgently a transplant is needed.[24]

Table 1. Contraindications to Liver Transplantation.*

Contraindications
Extrahepatic cancers, other than skin cancer
Anatomical abnormalities that preclude transplantation
Current illicit drug use
AIDS
Advanced cardiac disease (unless suitable for combined liver–heart transplantation)
Case-by-Case Assessment†
Sustained hemodynamic instability requiring high vasopressor administration
Large hepatocellular carcinomas or those with vascular invasion
Metastasis to the liver, from a treated extrahepatic primary tumor
Intrahepatic cholangiocarcinoma
Marked frailty
Fulminant hepatic failure with likely brain injury
Alcohol use disorder with recent consumption of alcohol
Current use of cigarettes
Inadequate social support
A history of frequent nonadherence to medical management
Lack of public or private insurance coverage
Conditions Not Considered to Be Contraindications
Advanced age (unless accompanied by frailty or other contraindications)
Obesity (unless accompanied by frailty or other contraindications)
Sepsis confined to the liver (e.g., hepatic abscess, ascending cholangitis)
HIV infection controlled by HAART

* AIDS denotes acquired immunodeficiency syndrome, HAART highly active antiretroviral therapy, and HIV human immunodeficiency virus.

† The impediments that are listed here result in an individualized pretransplantation assessment.

TRANSPLANTATION IN PATIENTS WITH CANCER

Patients with extensive HCC may become acceptable transplantation candidates after undergoing successful antitumor treatment to decrease tumor size, as shown radiologically, before transplantation.[25] In the United States, the percentage of transplantations performed in patients with HCC fell from 17.2% in 2010 to 12.6% in 2020 because after 2010, fewer patients were awarded exception points for having HCC.[3] Patients with other primary liver cancers, such as cholangiocarcinoma of the hepatic hilum or hemangioendothelioma, and in some circumstances, nonprimary liver tumors, such as neuroendocrine tumors or metastatic colon cancer, may also be considered suitable transplantation candidates (Table S1).

TRANSPLANTATION IN PATIENTS WITH ALD

In 1997, the American Society of Transplantation (previously known as the American Society of Transplant Physicians) and the American Association for the Study of Liver Diseases endorsed 6 months of abstinence as a prerequisite for placement of patients with ALD on the liver-transplant waiting list.[26] In 2011, Mathurin et al. reported that liver transplantation was lifesaving

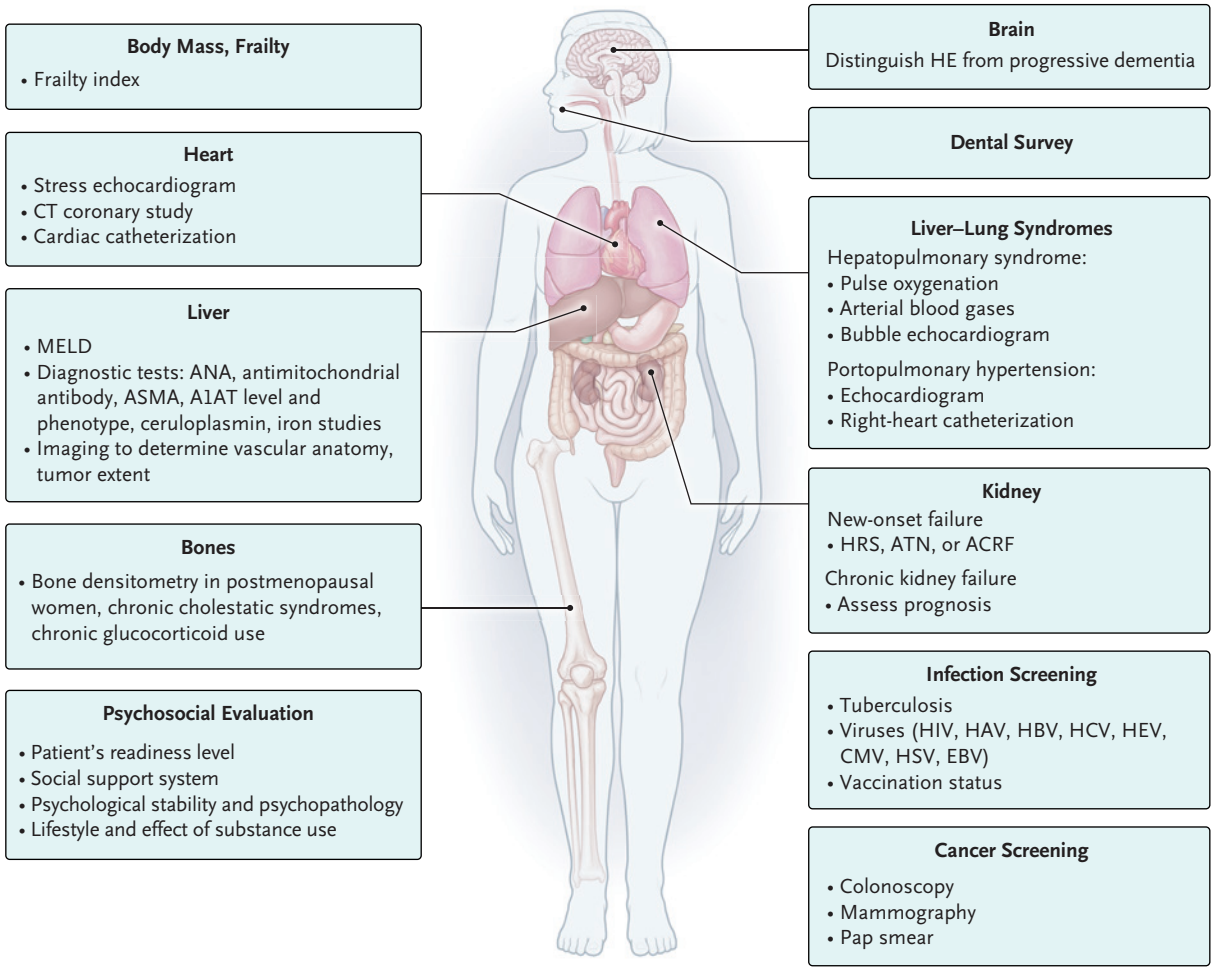

Figure 2. Components of an Evaluation for Liver Transplantation.

Pretransplantation assessment is individualized for each patient according to the diagnosis, degree of liver impairment, and risks associated with coexisting disorders affecting vital organ systems. A1AT denotes alpha-1 antitrypsin, ACRF acute-on-chronic renal failure, ANA antinuclear antibody, ASMA anti–smooth-muscle antibody, ATN acute tubular necrosis, CMV cytomegalovirus, EBV Epstein–Barr virus, HAV hepatitis A virus, HBV hepatitis B virus, HCV hepatitis C virus, HE hepatic encephalopathy, HEV hepatitis E virus, HIV human immunodeficiency virus, HRS hepatorenal syndrome, and HSV herpes simplex virus.

in a small, prospective European pilot study involving selected patients with severe alcohol-associated hepatitis that was unresponsive to medical therapy, an observation subsequently corroborated by a retrospective multicenter U.S. study.[27,28] According to current European and American guidelines, the selection of patients with ALD for liver transplantation should be based on a detailed psychosocial evaluation, preferably linked with management of alcohol use disorder, rather than on the 6-month abstinence rule.[29,30] Psychosocial evaluation includes assessment of the patient's history of treatment for alcohol use disorder, interest in pursuing sobriety, and social network for providing support for sobriety.[30] With the use of these guidelines, only a minority of potential ALD candidates are selected for placement on the waiting list. In a cohort of patients with ALD who had high MELD scores but limited sobriety, who were denied placement on the transplant waiting list, the 90-day mortality exceeded 50%, illus-

Table 2. Key Aspects of Living-Donor Liver Transplantation.*

Type of donation
Adult to child: often only left lateral segment of liver
Adult to adult: up to 70% of liver, along with intact vascular and biliary structures
Donor characteristics
May be related or unrelated to recipient
Must be acting voluntarily, with verification of donor's understanding of risks, benefits, and processes
Compatible blood type
Ideal age: 21–55 yr; donors 18–20 or 56–60 yr may be considered on a case-by-case basis
Preferred BMI: <35; if BMI is 30–35, weight loss may be needed
Donor evaluation
Liver anatomy and volume
Physical health, including hepatic and cardiopulmonary health, with cancer and infections ruled out
Emotional and mental health
Availability of support from family, friends
Consequences for donors
Serious injury, even death, on rare occasions
Less severe complications in up to 40% of donors
Postoperative recovery may require 3-mo absence from work

* BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

trating the life-or-death nature of the selection process in this population.[31,32]

ALLOCATION AND ACCEPTANCE OF LIVERS FROM DECEASED DONORS

The most recent policies governing allocation of deceased donor livers in the United States prioritize candidates on the waiting list according to their MELD or PELD scores and also their proximity to the donor hospital, in order to reduce inequities based on the geographic location of the recipient.[33] The assessment of the viability of a liver from a deceased donor has traditionally relied on the donor's history, as well as the biochemical function, gross appearance, and histologic evaluation of the liver. In the past, livers obtained with the use of extended criteria (livers from donors with various potential adverse issues, such as an age of >60 years, a positive test for HCV, abnormal liver-function tests, a stay in the intensive care unit [ICU] for >5 days, or treatment with medications to support blood pressure and livers with >30% large-droplet fat, as judged on histologic evaluation) were associated with higher rates of donor-liver dysfunction leading to graft loss and, in some cases, the death of the recipient.[34] Unfortunately, as many as 70% of livers from potential deceased donors in the United States and the United Kingdom are discarded on the basis of this subjective assessment.[35,36] Indeed, livers declined by one center may subsequently be transplanted successfully in a lower-priority patient at another center, indicating the need for better methods to estimate the viability of donor livers.[37]

EXPANDING THE POOL OF LIVERS FROM DECEASED DONORS

Most deceased-donor livers are from persons receiving life support who have irreversible cerebral and brain-stem injury (declared brain death). One strategy to expand the pool of usable donor livers is the use, in carefully selected circumstances, of organs from deceased donors infected by HCV or the human immunodeficiency virus. Another strategy is donation after circulatory death, with death declared on the basis of

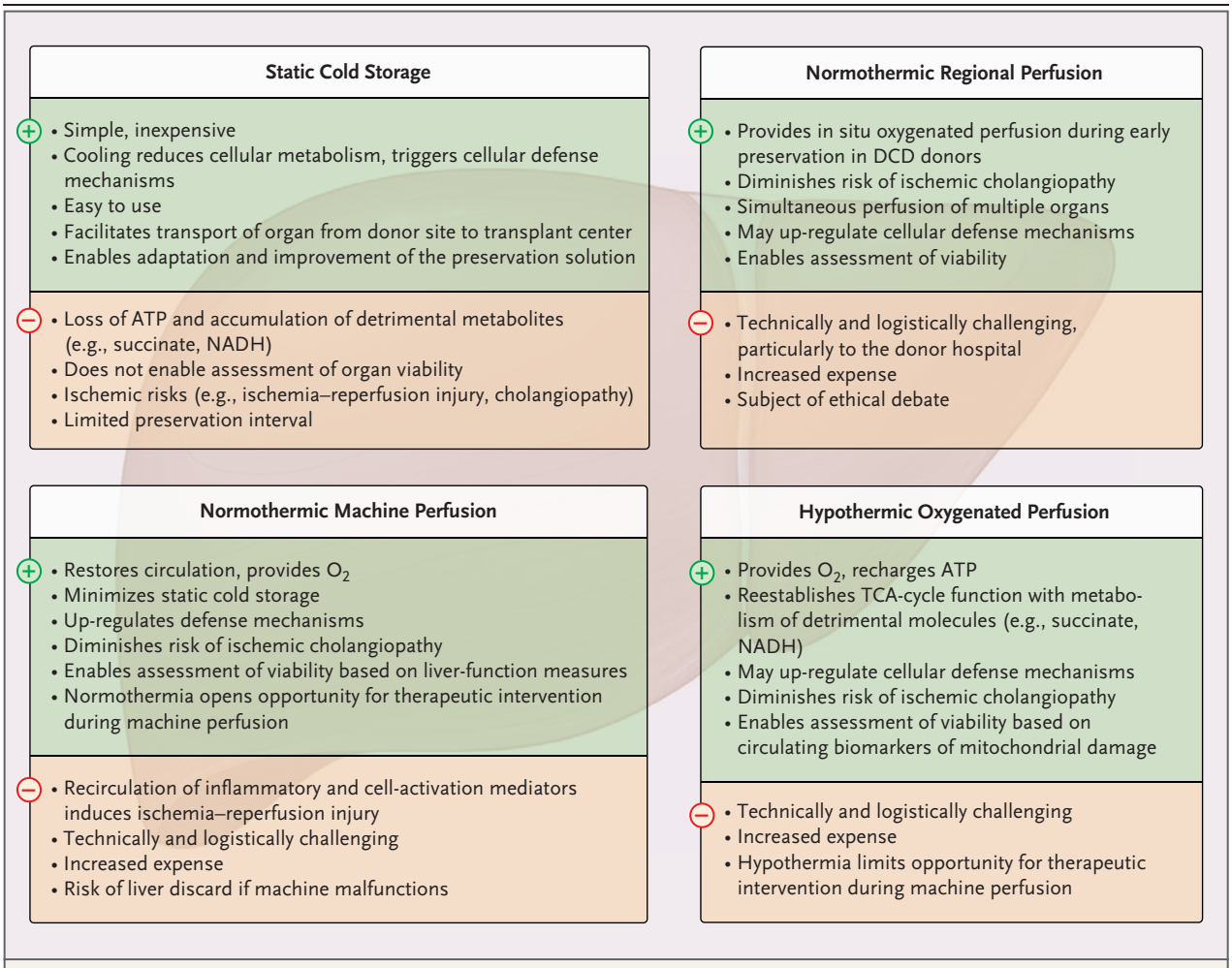

Figure 3. Approaches to the Management of Donor Livers before Transplantation.

The information is adapted from Widmer et al.[41] The plus symbol indicates potential benefits of the system, and the minus symbol indicates potential harms. DCD denotes donation after circulatory death, and TCA tricarboxylic acid.

the cessation of both circulatory and respiratory function in patients who retain brain-stem function, despite severe, irreversible neurologic injury. Uncontrolled donation after circulatory death refers to donation after circulatory arrest that occurred either before the patient's arrival at the hospital or after unsuccessful resuscitation in the hospital. In contrast, controlled donation after circulatory death refers to donation after withdrawal of life support under controlled circumstances in the hospital. The degree of injury to the liver is usually greater with uncontrolled donation after circulatory death, and controlled donation is the more commonly practiced approach worldwide.

There is an urgent need to increase the number of livers available for pediatric liver-transplantation candidates, especially infants. Given the ability of the liver to regenerate, one strategy that appears to be helpful is to split a liver from a deceased donor into two allografts, typically with one piece transplanted in a small child and the other in an adult. A study in the United Kingdom showed that a national "intention to split policy" has the potential to reduce mortality among children on the waiting list.[38]

MANAGEMENT OF DONATED LIVERS BEFORE IMPLANTATION

The standard of care for more than 30 years has been to flush the organ from a deceased donor with preservation solution at 4°C, in order to reduce cellular metabolic processes, and then to transport the organ to the transplantation site under conditions of static cold storage.[39] Even though static cold storage is effective, continued cold ischemia leads to mitochondrial changes, including decreased cellular respiration and the accumulation of succinate and NADH with concomitant ATP depletion. On reperfusion, reactive oxygen species are released from the mitochondria, leading to further cellular injury.[40,41] Ischemia–reperfusion injury occurring in the transplanted liver may cause clinically important hemodynamic changes and lead to tissue injury, particularly in higher-risk organs such as steatotic livers, older livers, and those recovered after circulatory death.

In contrast, machine perfusion before implantation aims to ensure more consistent tissue quality, while extending the preservation time and reducing the discard rate (Fig. 3).[42] Machine perfusion of donor livers with oxygenated solutions may mitigate ischemia–reperfusion injury and allow for successful transplantation of higher-risk livers.

Two ex vivo machine perfusion strategies currently used are hypothermic machine perfusion and normothermic machine perfusion. During hypothermic machine perfusion, the liver is dynamically perfused with the use of a standard cold preservation solution at 4 to 8°C and the addition of oxygen. Studies have shown that livers donated after circulatory death and treated with hypothermic oxygenated machine perfusion are associated with a significantly lower risk of intrahepatic biliary strictures, as compared with livers donated after circulatory death and maintained in static cold storage.[43,44]

Normothermic machine perfusion of the donor liver pumps oxygenated, ABO-compatible blood at 37°C through the hepatic artery and portal vein simultaneously. This approach has led to significant reductions in early allograft dysfunction and ischemic-type biliary strictures, as compared with static cold storage.[45,46] The viability of organs maintained with normothermic machine perfusion can be assessed by measuring oxygen use and the release of lactate and aminotransferases.

Normothermic regional perfusion refers to in vivo perfusion of donors after circulatory death with oxygenated blood through a mechanical circulatory device that provides extracorporeal membrane oxygenation.[47] With normothermic regional perfusion, the liver can be assessed soon after death is declared. This approach may increase the use of livers donated after circulatory death, with excellent outcomes.[47,48] Normothermic regional perfusion has been the subject of a robust ethical debate regarding the "dead donor rule," which states that a person must be declared dead before any vital organs can be removed for transplantation.[49,50]

Machine perfusion of organs from deceased-donor organs is costly and complicated. High-quality data comparing different perfusion options are lacking, as are data-based criteria for selecting the type of machine perfusion to use in place of standard cold storage. Similarly, whether it is better to perform machine perfusion at the hospital where the organ is recovered or to transport the liver in static cold storage to the transplantation center before machine perfusion is used requires clarification.

OUTCOMES AFTER LIVER TRANSPLANTATION

From 1988 through 2022, slightly more than 200,000 liver transplantations were performed in the United States, and as of June 30, 2020, a total of 98,989 liver-transplant recipients were alive.[3,5] A liver-transplant recipient is best cared for by a multidisciplinary team at a transplantation center. The team, comprising a hepatologist, a surgeon, an interventional radiologist, and a specialist in transplant-related infectious disease, works collaboratively with the patient's primary care provider, particularly regarding health maintenance, many features of which are altered by long-term immunosuppressive therapy.

Every patient undergoing liver transplantation is at risk for unfortunate outcomes such as perioperative death, the ischemia–reperfusion injury

syndrome (described above), and primary allograft nonfunction or early poor function of the allograft, as well as acute kidney injury. Patients who have higher MELD scores, who are frail, or who are recipients of higher-risk allografts tend to have prolonged stays in the ICU and the hospital.[51] The long-term care of a transplant recipient entails support for the maintenance of a healthy body-mass index, management of systemic hypertension and diabetes, regular surveillance of bone health, and cancer screening.[52] Surveillance for recurrence of liver disease is required if the indication for transplantation was viral hepatitis, an autoimmune liver disorder, alcohol use disorder, MASLD, or primary liver cancer.

The expected 1-year patient and graft survival rates after primary liver transplantation in adults are 94 and 92%, respectively.[3] The mean estimated survival of patients who received transplants in the 1990s is 20 years.[53] The 1- and 10-year patient survival rates for recipients of liver transplants in childhood are 94.4 and 90.7%, respectively, and pediatric graft survival rates for the same intervals are 90.9 and 79.1%.[3] Patient survival is similar after receipt of a liver transplant from a controlled donation after circulatory death and donation after declared brain death, but recipients of transplants after circulatory death are more likely to have allograft-related morbidity. Adult recipients of a split-liver allograft have excellent long-term patient and graft survival rates, as compared with adult recipients of a whole-liver allograft, although split-liver allografts are associated with increased rates of hepatic-artery thrombosis and biliary complications.[54,55] Pediatric recipients undergoing liver transplantation with a split, reduced, or living-donor graft (technical variant grafts) from an adult donor have decreased odds of developing hepatic artery thrombosis as compared with those who receive a whole liver from a deceased pediatric donor, whereas portal-vein complications and biliary strictures are more likely to occur with the transplantation of technical variant grafts.[56-58]

Surgical complications arising in the first 90 days after transplantation can be divided into three main groups: biliary, vascular, and hemorrhagic complications. Biliary ischemia causes intrahepatic biliary strictures, bile lakes (or bilomas), and bile-duct casts, collectively termed ischemic cholangiopathy.[59] This disorder occurs more frequently in recipients of livers donated after circulatory death than in recipients of livers donated after declared brain death. Biliary complications are managed by means of endoscopic retrograde cholangiopancreatography, percutaneous drainage, or reoperation, and vascular complications are addressed through angioplasty and stenting, medications, or reoperation, with the specific approach varying according to the expertise at each center.

ALLOGRAFT REJECTION AND IMMUNOSUPPRESSION

The definitive diagnosis of T-cell–mediated rejection requires a liver biopsy.[60,61] The incidence of T-cell–mediated rejection within the first 90 days after liver transplantation ranges between 10 and 30% but is subsequently lower, with an incidence of just 3% after the first year.[3,62] Biopsy-proven T-cell–mediated rejection carries a clinically important increased risk of graft loss and death, particularly when it occurs more than 1 year after transplantation, sometimes on account of progression to vasculopathic bile-duct obliteration, referred to as chronic rejection.[62,63] The standard therapy for moderate-to-severe T-cell–mediated rejection is a 3-day course of high-dose glucocorticoids, such as methylprednisolone (10 mg per kilogram of body weight per day, or up to 1 g per day for 3 days). The use of other therapy, such as antilymphocyte antibodies, is reserved for severe rejection that does not respond to glucocorticoid therapy. The role of antibody-mediated rejection in liver transplantation remains controversial (Table S4).[64,65]

A typical maintenance immunosuppressive protocol comprises a calcineurin inhibitor such as tacrolimus, often with mycophenolate, prednisone, or both.[3] Every immunosuppressive agent has adverse effects (Table S5). Immunosuppression is reduced gradually during the first 3 to 6 months after transplantation, as the risk of T-cell–mediated rejection declines. A state of tolerance that is sufficient to permit complete withdrawal of immunosuppressive therapy oc-

curs in less than 5% of long-term survivors of liver transplantation.[63]

INFECTIONS IN LIVER-TRANSPLANT RECIPIENTS

Infections after transplantation may be due to reactivation of a latent infection in the recipient, transmission of an infectious agent by the allograft, or acquisition of a new infection in the recipient.[66] The potential for infections varies according to the interval since surgery, the use of prophylaxis against specific organisms, and the degree of immunosuppression (Table S6).[66] In the early period after transplantation, surgical complications that affect vascular or biliary anastomoses, poor wound healing, or organ failure resulting in prolonged assisted ventilation or kidney replacement therapy increase the risk of infectious complications.[66] After the first month, there is an increased risk of opportunistic infections such as cytomegalovirus, pneumocystis, and aspergillus infections. These risks are mitigated by prophylactic antimicrobial therapy during the intervals of greatest risk. Neutropenia, which increases susceptibility to bacterial infection, is common after liver transplantation, exacerbated by drugs that are given after transplantation such as mycophenolic acid, valganciclovir, and cotrimoxazole. After the first 6 months, a reduction in maintenance immunosuppressive therapy generally lowers the risk of opportunistic infection, whereas treatment of cellular rejection, if it occurs, increases the risk.

CANCER RISK AMONG LIVER-TRANSPLANT RECIPIENTS

Patients who undergo transplantation as therapy for cancer in the native liver are at risk for a recurrence of the cancer in the transplanted liver. In addition, the interaction of immunosuppression with factors associated with de novo oncogenesis may lead to skin cancers due to sun exposure; aerodigestive cancers in cigarette smokers; colon cancer, particularly in patients who undergo transplantation for primary sclerosing cholangitis; and virus-associated cancers, such as cervical cancer or post-transplantation lymphoproliferative disorder (Table S6).[66,67]

TRANSITION OF CARE FOR CHILDHOOD LIVER-TRANSPLANT RECIPIENTS

The transition from pediatric care to adult care for persons who received a liver transplant in childhood encompasses a period of vulnerability for young adults, during which medication adherence, decision-making, and communication skills have not yet fully matured.[68,69] The American Society of Transplantation has established a Pediatric Transition Portal, which provides clinicians with readiness assessment tools and checklists to assist adolescent and young-adult transplant recipients in the transition to adult care.[70]

THE FUTURE OF LIVER TRANSPLANTATION

Liver transplantation will probably remain the treatment of last resort for life-threatening liver disease for some years to come. The evolution of new treatments for serious liver disease or, more fundamentally, a reduction in the social influences that drive the two liver diseases known to be related to consumption (MASLD and ALD) would reduce the demand for transplantation. Better tools for identifying patients with ALD who are likely to recover without transplantation, better instruments for predicting future drinking, and studies of alcohol use disorder in patients with ALD will advance the care of patients. A straightforward improvement would be for centers to be more candid with patients and their families about the process of selection for transplantation.[71] We hope that the continuing need for immunosuppression will stimulate the development of methods to induce selective tolerance in patients with liver allografts.[72] The discrepancy between the supply of and demand for donor livers will probably persist for the foreseeable future. Machine perfusion of donor livers, as discussed above, may offer the best hope for increasing the donor liver supply through dynamic assessment of allograft viability and the application of therapies to recondition the allograft before implantation.[42] We await breakthroughs that might come through the use of xenografts or tissue engineering.[73,74]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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